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Review Article

Occupational Exposures and Reproductive Health: 2003 Teratology Society Meeting Symposium Summary

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Assuring reproductive health in the workplace challenges researchers, occupational safety and health practitioners, and clinicians. Most chemicals in the workplace have not been evaluated for reproductive toxicity. Although occupational exposure limits are established to protect 'nearly all' workers, there is little research that characterizes reproductive hazards. For researchers, improvements in epidemiologic design and exposure assessment methods are needed to conduct adequate reproductive studies. Occupational safety and health programs' qualitative and quantitative evaluations of the workplace for reproductive hazards may differ from standardized approaches used for other occupational hazards in that estimates of exposure intensity must be considered in the context of the time-dependent windows of reproductive susceptibility. Clinicians and counselors should place the risk estimate into context by emphasizing the limitations of the available knowledge and the qualitative nature of the exposure estimates, as well as what is known about other non-occupational risk factors for adverse outcomes. This will allow informed decision-making about the need for added protections or alternative duty assignment when a hazard cannot be eliminated. These policies should preserve a worker's income, benefits, and seniority. Applying hazard control technologies and hazard communication training can minimize a worker's risk. Chemical reproductive hazard training is required for workers by the Occupational Safety and Health Administration's Hazard Communication Standard. The National Institute for Occupational Safety and Health (NIOSH) has formed a National Occupational Research Agenda Team to promote communication and partnering among reproductive toxicologists, clinicians and epidemiologists, to improve reproductive hazard exposure assessment and management, and to encourage needed research. *Birth Defects Res B* 74:157–163, 2005. Published 2005 Wiley-Liss, Inc.

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INTRODUCTION

The promotion of reproductive health in the workplace presents unique challenges to researchers, occupational safety and health professionals, and clinicians. Josef Warkany, founder of the Teratology Society, was prescient over 50 years ago when he said, "…the fetus should be assured so far as possible by protection of the expectant mother from adverse environmental influences" (Warkany, 1950).

A strong argument can be made for the substitution of "worker" for "expectant mother" in his quotation. As of 2002, 55% of children were born to working mothers (U.S. Census Bureau, 2003), and 65% of employed men and women were of reproductive age in 2001 (U.S. Census Bureau, 2002). There is a large potential for occupational hazards to impact the reproductive health of these workers, who spend roughly a third of their lives in the workplace. Approximately 84,000 chemical compounds are in the workplace, with 2,000 new chemicals introduced each year. By comparison, only about 4,000 chemicals have been evaluated for reproductive toxicity (U.S. Environmental

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Protection Agency, 1998). Absence of sufficient toxicologic and epidemiologic data lends uncertainty as to the magnitude of risk a specific toxicant presents. Further, the majority of chemical toxicants regulated by public health agencies charged with assuring safety and health in the workplace have not been evaluated for reproductive endpoints (U.S. General Accounting Office, 1991). This gap in the regulatory safety net allows reproductive toxicants to be encountered in work settings by both male and female workers. Several employment sectors where reproductive and developmental toxicants occur require intervention strategies to minimize their impact on health to male and female workers. Examples include manufacturing settings such as the electronics industry that use heavy metals (lead, cadmium) and organic solvents (glycol ethers, toluene). Other toxicants include pesticides and herbicides used in agriculture (ethylene dibromide) and sterilant anesthetic gases and anti-cancer drugs used in healthcare. Female workers predominate in some of these sectors, including laboratory and clinical medicine, printing, and dry cleaning (Stellman, 1994).

Not only are there a large number of potential exposures that may adversely affect health, but accurate assessment of multiple workplace exposures becomes complex when specific time-dependent windows of reproductive susceptibility are considered. Communication of reproductive risks to workers is correspondingly complex.

The National Institute for Occupational Safety and Health (NIOSH; one of the Centers for Disease Control and Prevention) introduced the National Occupational Research Agenda (NORA) in 1997 to promote, leverage, and facilitate occupational research, and to define and implement a research agenda for the next decade. NORA is comprised of 21 teams of industry, academic, and government experts in occupational health. The research agenda of the NORA Reproductive Health Research Team specifically encourages communication and partnering among reproductive toxicologists, clinicians, and epidemiologists (Lawson et al., 2003).

Because of the challenges in assessing workplace reproductive hazards, the NORA Reproductive Health Research Team sponsored a symposium at the 2003 Annual Meeting of the Teratology Society. The content of this symposium, summarized in this article, provided an overview of practical aspects of occupational reproductive hazard exposure assessment as applied to epidemiologic studies, safety and health programs in the workplace, and clinical practice.

Epidemiologic Studies

As epidemiologists develop and refine methods to study human reproductive effects, they continue to investigate potential occupational reproductive hazards. Human studies that provide evidence of a relation between occupational exposures and adverse reproductive effects are extremely difficult to conduct because of cost, time, and the processes required to identify the hazard and assess exposure. There are intrinsic methodologic limitations in interpreting observational human studies. However, aspects of epidemiologic design can be improved to maximize the quality of these studies. These include testing specific a priori hypotheses, appropriate adjustment for other factors, and determination of a dose–response relationship if present (Swaen et al., 2001).

The public face of epidemiology is often distorted in the media. Obvious offenses include ''risk-factorology'' (assigning risk factor status to an individual based on the myriad tests of exploratory analyses [''fishing expeditions'']); ''black box association'' (assigning causation when a causal mechanism is unknown or considered irrelevant); and a focus only on individual risks, rather than locating associations within their historical, political, and social context (Smith, 2001). Warkany may have been thinking about epidemiology when he said, ''...we must consider our methods...not only emphasize frontal attacks but also consider less glamorous indirect methods'' (Warkany, 1985).

Individual birth defects are relatively rare, but birth defects are collectively the number one cause of U.S. infant deaths (Pew Environmental Health Commission, 2000). Epidemiologists have begun to improve the field's ''less glamorous indirect methods'' by confirming diagnoses, more precisely assessing exposures, and controlling for potential confounders. Even so, much more research is needed. It is generally stated that toxicants, including those from occupational and environmental sources, are responsible for at least 3–10% of major birth defects. This figure is at best an estimate. Occupational exposures may be responsible for some of the nearly half of all birth defects that are of unknown etiology (Brent and Beckman, 1994; Bishop et al., 1997).

To gain information about etiology and prevention of birth defects, surveillance resources need to be enhanced. More precise study designs, such as case-control studies, need to be supported, as well as more accurate birth defect ascertainment. A national registry or large, high quality state registries are necessary to adequately study rare birth defects. The Pew Commission recently graded existing state registries (Pew Environmental Health Commission, 2000). Grades of C or lower were given to 57% of the registries; only 15% of registries earned an ''A'' grade. The rare disease/rare exposure associations between birth defects and occupational exposures require not only a case-control study design but also the best available precision and accuracy for exposure assessment (Bracken, 2001).

Exposure assessment information collected for reproductive studies can include work histories, agent checklists, and detailed questionnaires. These components of exposure assessment may change depending on the nature of the industry and exposures being studied. For example, a recent study of workers in the semiconductor industry, which found an association between exposure to glycol ethers and miscarriage rates, used an ordinal exposure classification scheme based on job titles and industrial hygiene monitoring results (Correa et al., 1996). Another study found an association between congenital malformations and self-reported occupational exposure to solvents from interviews with the individual study subjects (Khattak et al., 1999). Each of these methods has limitations compared to an idealized biomarker collected during the appropriate time window of exposure for a specific reproductive event.

Because of the relatively short time period between exposure and the effect, as well as the critical importance of the timing of exposure, epidemiology studies of reproductive hazards have provided a context for methodological research on exposure assessment. In a case-control study of mothers of children with spina bifida, a comparison found that postal questionnaires resulted in overestimation of exposure compared to face-to-face interviews, and the authors recommended that job-specific interviews (whose questions focus on specific tasks or processes of a single job) be carried out whenever possible to improve specificity in population based case-control studies (Blattner et al., 1997). A study of risk factors for male infertility compared several different methods for assessing exposure to aromatic solvents, including self report, job exposure matrices (a method for categorizing multiple jobs to exposure levels for chemical, physical, or biological agents based on current knowledge of each job's exposures), job-specific questionnaires, as well as air and urine samples. The job-specific questionnaires provided discrimination between high and low exposures and the highest predictive values for biological monitoring results (Tielmans et al., 1999).

The greater attention to timing required to assess occupational exposures to reproductive hazards as compared to other types of health hazards represents a challenge to epidemiologists and industrial hygienists. This challenge has led to recognition of the need for improvement in monitoring strategies and techniques, and has provided motivation to improve exposure assessments for epidemiology studies of reproductive hazards.

Safety and Health Programs in the Workplace

Managing reproductive hazards in the work setting first requires hazard identification. Application of the classical industrial hygiene hierarchy of control technologies (engineering or enclosing hazardous processes, work practice controls, and use of personal protective equipment (PPE) such as protective clothing and respirators) can then be exploited to minimize worker exposure. The American College of Occupational and Environmental Medicine (1996) has issued "Reproductive Hazard Management Guidelines" to assist occupational health professionals in mitigating worker exposure.

Employers have a responsibility to meet legal requirements in providing a workplace that is free of recognized health hazards. A specific occupational exposure may or may not be of clinical significance with respect to reproductive hazards; however, because people spend a significant length of time at work, and pregnancy is often associated with a heightened level of concern and anxiety, they may often regard the workplace as a threat to their ability to conceive and bear healthy offspring. A successful occupational health and safety program must promptly recognize and adequately address these concerns, regardless of the level of actual risk. The capability to respond to worker concerns requires a cooperative approach that includes management support and worker participation, as well as proactive workplace evaluations for reproductive hazards by safety, industrial hygiene, and medical professionals.

The methods used to conduct workplace exposure assessments for reproductive health hazards are in many ways similar to the methods used for the assessment of other types of health hazards. For many substances, exposure can result in a range of different acute or chronic adverse health effects depending on the timing and intensity of exposure, as well as the susceptibility of the individuals exposed. This is especially true for exposure to reproductive hazards, which may not result in acute symptoms yet may adversely affect fertility or fetal development. The limitations and uncertainty in our current level of knowledge about reproductive hazards requires an extra level of diligence on the part of the industrial hygienists when developing strategies for evaluating the workplace and when interpreting exposure monitoring results.

The recognition of reproductive hazards begins with a qualitative evaluation of the workplace. A checklist like that in Figure 1 could be used to initiate an investigation. This information could be developed into a complete list of potential hazards present regardless of the intensity or severity of exposure. This hazard inventory can then be compared to lists of known or potential reproductive hazards. Under the OSHA Hazard Communication Standard (1910.1200; U.S. Department of Labor, 1990), employers are required to develop and maintain a hazardous chemical inventory. Hazardous ingredients, including reproductive hazards, must be listed on Material Safety Data Sheets (MSDS) if present at concentrations $>1\%$. Thus MSDS are valuable sources of information for establishing the use or presence of specific chemicals and thus a potential for exposure. There are, however, exclusions for trade secrets, the exact identity of certain ingredients are not always disclosed, and the quality of MSDS is highly variable (Paul and Kurtz, 1994).

The National Institute for Occupational Safety and Health (1999, 2004) and the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (2004) provide excellent publications to assist with identification of reproductive hazards that are made available through their web sites. These publications include lists of chemical and physical agents that are known or suspected to be reproductive hazards. The National Library of Medicine offers a "Haz-Map" site (http://hazmap.nlm.nih.gov/) that provides initial information on numerous occupational hazards, including reproductive toxicants. Non-governmental organizations such as the Teratology Society, the Organization of Teratology Information Services (OTIS), and the American College of Occupational and Environmental Medicine (ACOEM) also provide lists and other valuable information for identification and recognition of reproductive hazards in the workplace.

When qualitative evaluation identifies the presence of a reproductive hazard, then a more thorough quantitative evaluation by an occupational health professional may be needed to assess the potential severity of the hazard (Fig. 2). Only a broad approach to this process is presented. The quantitative assessment of reproductive hazards may require a more detailed approach than other types of health hazards. Although many of the assessment methods are similar to those for other occupational exposures, reproductive exposure timing issues are focused on specific short-term intervals, and most occupational exposure limits are not designed to protect the reproductive process, including the fetus. For instance, the measurement of 8-hr time weighted average exposure levels for comparison with occupational exposure limits is not sufficient for the evaluation of reproductive health hazards. Another example is that an industrial hygienist will often attempt to identify groups

Is the worker exposed to:

Chemical Agents
- ☐ Inorganic chemicals
- ☐ Organic solvents and fuels
- ☐ Metals - lead, cadmium, mercury
- ☐ Pesticides
- ☐ Other (specify)

Physical Agents
- ☐ Ionizing Radiation
- ☐ Microwave and other RF radiation
- ☐ "Noise" (intense sound)
- ☐ Thermal stress (heat or cold)
- ☐ Vibration
- ☐ Other (specify)

Biological Agents
- ☐ Bacteria
- ☐ Fungi
- ☐ Viruses
- ☐ Protozoa
- ☐ Animal danders
- ☐ Endotoxins
- ☐ Enzymes / proteins
- ☐ Other (specify)

Physical Conditions
- ☐ Irregular or shift work
- ☐ Strenuous work
- ☐ Prolonged standing/lifting
- ☐ Other hazards (specify)

Specify agents or conditions here:

Fig. 1. Example checklist for initial qualitative evaluation of reproductive hazards.

- ☐ Frequency (number of exposures per shift)
- ☐ Duration (of exposure; work shift)
- ☐ Air Concentration / Intensity of Exposure (units)
- ☐ Peak, Time-Weighted Average
- ☐ Timing (relation of exposure to critical time windows)
- ☐ Route of Exposure (Inhalation, Dermal, Ingestion)

Fig. 2. Example of checklist for initial quantitative evaluation of reproductive hazards.

of workers with similar exposures, and then conduct exposure monitoring for just a few workers who are assumed to be representative of the entire group. When addressing worker concerns about reproductive hazards, however, it is important for the industrial hygienist to take the extra time and effort required to understand the job duties and the patterns of exposure of a particular individual. Short term peaks or unique circumstances in exposures may be of greater significance with respect to reproductive hazards than the long term average exposure level. Job duties and patterns of exposure can be important for other occupational diseases, but reproductive hazard exposures may be described in intervals as short as a few days or weeks.

Also inherent in a comprehensive approach to reproductive hazards management is the Occupational Safety and Health Administration's (OSHA) Hazard Communication Standard (Haz Com) requiring employer training of workers regarding the health effects of chemical hazards on the job, and ways to minimize exposure. This standard also requires worker training on chemicals causing reproductive effects. (U.S. Department of Labor, 1990).

Communicating reproductive health risk to potentially exposed workers allows affected employees to make informed decisions about work exposure as they contemplate or experience a pregnancy or during other potentially vulnerable periods such as during breastfeeding. During the "haz com" mandated worker education sessions other risk management options can be discussed with affected workers including medical surveillance, which complements control technologies, especially when a hazard cannot be eliminated. (McDiarmid and Curbow, 1992). This can be as simple as a self-administered annual health questionnaire including reproductive outcomes, providing passive surveillance data to the employee health unit. Other administrative policies such as "worker notification of pregnancy" to the employee health unit provide the opportunity for counseling and consideration of alternative duty and temporary reassignment of work. This notification of pregnancy action is the basis for the Quebec government's "retrait preventiv" (protective reassignment) program of protective alternative duty or medical leave for pregnant workers (McDonald, 1994). These policies should preserve a worker's income, benefits and seniority and may be governed by federal and state employment, disability, worker compensation and pregnancy discrimination laws that should be consulted in crafting a reproductive health policy (Kaczmarczyk and Paul, 1996; Feitshans and Mues, 2002).

Occupational exposure limits are established to protect "nearly all" workers, but are not necessarily protective for susceptible subgroups including the fetus. Thus, the definition of an acceptable or "safe" exposure for reproductive hazards is not well understood, and therefore involves a subjective judgment by an occupational health professional that must be ethically, legally, and scientifically defensible. In this situation, the industrial hygienist can provide information on exposure levels, but not necessarily whether the exposures are acceptable for a specific individual.

Clinical Tools and Strategies

Clinical tools in settings such as patient care or telephone counseling by a teratogen information service can be used to focus on the most important aspects of a complex occupational exposure history. The level of exposure conveyed by a specific job can be estimated by using a systematic approach. To help assemble a complete list of potentially important exposures, workers can be asked to fill out forms, or the professional taking the history can use a checklist (Frazier and Hage, 1998; Carter et al., 2000). The types of exposures to consider include chemical, biological, and radiological agents, as well as job related ergonomic demands, circadian rhythm disruption and other kinds of potential risks. Because many workers do not know what toxicants they work with, information on tasks should also be collected. Task information can then be evaluated by an occupational health professional for possible exposures. The exposure history should assess not only exposures in the workplace but also non occupational exposures. These include hobbies, living on a farm, painting rooms in a house, and washing contaminated clothing.

In addition, a reproductive risk assessment should include both the women and the men. Even though men are susceptible to adverse reproductive effects from certain toxicants, men present with concerns about exposures much less often than women (Frazier and Jones, 2000; Felix et al., 2003), so the professional needs to ask about both members of the couple.

Although a person's work history may include multiple jobs, the most important exposures for assessing reproductive risks are thought to be those that occur in the 3–4 months before conception and during pregnancy and lactation. This is because most reproductive toxicants are believed to act through an acute toxicity mechanism in the periconceptual period or in critical periods of fetal or infant development (Selevan et al., 2000; Kimmel and Makris, 2001). Some exposures in the distant past, however, can potentially exert reproductive effects. For instance, pregnancy mobilizes maternal lead stores from bone that can then expose the fetus (Gulson et al., 1999; Brown et al., 2000). Fetal exposures can also occur from accumulated maternal stores of persistent chemicals such as dioxins and PCBs (Muckle et al., 2001; Vreugdenhil et al., 2002).

The worker will often report chemical exposure agents by product names. Chemical names can be obtained from product labels and Material Safety Data Sheets (MSDS). The health information on MSDS is of highly variable utility (Rosenstock and Cullen, 1994; McElveen and Beck, 1994; Carter et al., 2000; Frazier et al., 2001). In a study of reproductive health information on MSDS, products containing lead or ethylene glycol ethers were assessed (Paul and Kurtz, 1994). These compounds can affect the male and female reproductive systems. In more than one-third of the sheets, reproductive effects were not mentioned. When the potential for adverse reproductive outcomes was described, female effects were 18 times more likely to be listed than male effects.

Working with an agent is not the same as receiving an internal dose that results in a clinically detectable adverse health outcome. Factors in the exposure history that suggest a higher potential for internal dose include: 1) frequent contact; 2) use of larger quantities; and 3) characteristics that promote inhalation exposure or skin contact, such as aerosolization, distribution of fine powders into the air, or splashes of liquid products. Consuming food, drink, and tobacco products in the workplace can increase exposure levels if these items are likely to become contaminated by dusts, aerosols or splashes. Contaminated clothing taken home can expose family members (Curl et al., 2002). Use of personal protective equipment such as gloves or respirators can reduce internal dose, but can also be a sign of higher-exposure jobs where a break in technique could lead to internal dose.

After ascertaining the types of exposures and estimating exposure levels, a literature review using a variety of data sources is needed. The goal of the literature search is to assess whether the worker's exposures, at the levels of exposures estimated and during the time periods in which exposure occurred, have been linked with pertinent adverse outcomes. These adverse outcomes of male or female exposure could include subfecundity, spontaneous abortion, birth defects, other problems during pregnancy or adverse effects on fetal or infant development. Because the number of fully characterized reproductive toxicants is very small, additional approaches can be considered, including interpretation of available data and structure-activity relationships. The worker should be given an explanation of whether the level of risk seems to be negligible, modest or potentially high based on the estimate of exposure levels and the timing of exposure. Counseling should place the exposure estimate into context by emphasizing the limitations in the available reproductive and developmental research and the qualitative nature of exposure estimates, as well as what is known about other non-occupational risk factors for adverse outcomes. With the clinician or counselor, the worker can then make an informed decision about the best course of action.

CONCLUSIONS

A comprehensive response by public health entities is required to mitigate the negative health effects of occupational reproductive hazards. Awareness of reproductive hazards both by the healthcare community and the workers themselves is a first step in achieving a comprehensive response. Enlarging the expert healthcare community's knowledge beyond awareness to the epidemiology and toxicology of work-related reproductive and developmental toxicants is a key early strategy for intervention. Practical management policies for 'at risk' workers are also valuable tools.

The NIOSH NORA Reproductive Health Research Team has implemented three approaches to improve occupational reproductive health research and practice: facilitate collaboration with biologists, toxicologists, clinicians, and epidemiologists; improve reproductive hazard exposure assessment and management; and encourage the design and conduct of occupational reproductive health studies. Team members have suggested concepts for several grant announcements with other federal agencies for human occupational reproductive health studies, participated in the prioritization of reproductive toxicants (Moorman et al., 2000), and initiated a Hazardous Drug Working Group to improve instructions for use of antineoplastic agents in the hospital and for home health care. Results from these efforts will help researchers design epidemiologic studies that have the best prospects for interpretable results. NORA-funded projects are improving the quality of birth defects research by conducting exposure assessment for analyses of parental occupation from the National CDC Birth Defects Prevention Study, and by conducting large biomonitored surveys of pesticide exposure (with the National Institute of Environmental Health Sciences) and phthalate exposure (with CDC National Center for Environmental Health). A renewed focus on worker outreach activities to communicate reproductive hazards is also planned.

Interdisciplinary forums such as the symposium this article summarizes are also a strategic opportunity to share information, clarify misunderstandings, and describe knowledge gaps that suggest a research agenda for the coming years. Enlarging our capacity to protect the public's reproductive and developmental health at work can then be more successfully realized.

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